Supplementary file 2: AMETIS trial statistical analysis plan

Populations

Primary analysis will be done in modified intention to treat (ITT). Then, a per-protocol analysis will also be done to take into account protocol deviations notably crossover from CS to GA. Patients who withdraw consent will not be included in the analysis.

Intention-to treat (ITT) population: All randomised patients. This population will not be analysed in the AMETIS study.

Modified intention-to-treat population: All randomised patients except patients who:

- Withdrew consent for the use of data

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion.

Per-protocol population: All randomised patients except patients having one or more major protocol violations defined as:

- Patients who would not be eligible for randomization according to inclusion/non-inclusion criteria

  OR

- Patients who accidentally would have received the wrong intervention (CS or GA)

  OR

- Would never have any of the intervention (CS nor GA, for example due to spontaneous or thrombolytic associated reperfusion after randomisation but before the anaesthetic procedure)

  OR

- Would have the intervention (CS or GA) without any attempt of mechanical thrombectomy due to spontaneous or thrombolytic associated reperfusion

  OR

- Patients who would be withdrawn from the protocol because the patient would have withdrawn consent.

Statistical analyses

Primary analysis

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. For rate data, the generalized linear (Stata software: command glm) model will be used with Poisson distribution (link=log and offset), including a random effect to account for centre effect. Results will be expressed as Relative Risks and 95% confidence intervals.

Secondary analyses

- For the primary outcome

Multiple logistic mixed regression will be used with the following covariates (criterion for entering variables tested in the model will be selected if $P<0.10$ and according to clinically relevant covariates with anticipated relationship with outcome), including stratification

parameters, centre treated as a random effect. Particular attention will be paid to the study of multicollinearity.

Binary covariates

- Gender M/F
- Comorbidities Y/N
- Anticoagulation therapy Y/N
- Antiplatelet therapy Y/N
- Intravenous thrombolysis Y/N (stratification variable)
- Wake up stroke Y/N
- Quality of reperfusion: mTICI (good or bad)
- Left sided stroke Y/N
- Carotid top occlusion Y/N

Continuous covariates (with logarithmic transformation when appropriate)

- Demographic data
- Time delays

Ordinal covariates

- NIHSS score (stratification variable)
- Baseline mRS
- ASPECT score
- Localisation of AIS
- mTICI score

- For secondary outcomes

A chi-squared test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome (mRS score 0 to 2 by day 90, perioperative complications: intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7). Adjusted analyses will be performed with the use of random-effect Poisson generalized linear model regression and will be presented as Relative Risks and 95% confidence intervals, using the same adjustment variables.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables and center as random-effect. Results will be expressed as regression coefficients and 95% confidence intervals.

Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure, this parameter will be treated by different ways according to literature notably as an ordinal variable. A shift analysis will be also performed with Cochrane Mantel–Haenszel for the univariate analysis and random-effects ordinal logistic regression adjusted on initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion) for **multiple regression**.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For **multiple regression**, marginal Cox proportional hazards mode, with centre as random-effect, will be performed with results reported as hazard ratios with 95%

confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals.

Concerning the study of the parameters collected longitudinally, mixed models will be used to take into account between and within patient variability, in addition to centre random-effect. The following fixed effect will be analysed: randomisation group, time and their interaction.

Planned subgroup analyses will be done to explore potential influence of age, stroke laterality, stroke initial severity based on NIHSS, time delay, thrombus location and associated extracranial carotid artery stenosis/thrombosis on the incidence of the primary outcome. The study of interaction between randomization group and subgroup will be analysed.

If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method (Stata software, command mi).

A two-sided P value of less than 0.05 will be considered for statistical significance.

As proposed by some statisticians,[1,2] a particular focus will be given to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Outcomes

Primary outcome measure: The primary outcome measure is a composite of functional independence at 3 months and absence of perioperative complication occurring by day 7 after endovascular therapy for anterior circulation AIS. Functional independence is defined as a mRS score 0 to 2 by day 90. Perioperative complications are defined as intervention-associated arterial perforation or dissection, pneumonia or myocardial infarction or acute cardiogenic pulmonary oedema or malignant stroke evolution occurring by day 7.

Secondary outcome measures:

- Due to the lack of consensus concerning the categorisation of mRS as a stroke outcome measure[3,4]:
    - Ordinal score on the mRS by day 90
    - Functional independence by day 90 defined as a mRS score 0-2
    - Excellent recovery by day 90 defined as a mRS score 0-1
    - Moderate recovery by day 90 defined as a mRS score 0-3
    - Shift analysis of day 90 mRS adjusted for initial prognostic factors (baseline mRS, age, initial NIHSS, carotid top occlusion)
    - Good recovery defined with sliding dichotomy responder analysis relating day 90 mRS with baseline NIHSS score: mRS 0 for NIHSS ≤ 7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS > 14
- Intraprocedural hemodynamic and ventilatory conditions and complications defined as hypotension, blood pressure variability, hypoxemia and aspiration
- Intervention-associated vessel and others complications defined as arterial dissection or perforation, groin hematoma, embolization in another arterial territory
- Stroke onset to door delay, door to groin puncture delay, door to reperfusion delay, stroke onset to groin puncture delay, GA/CS induction to groin puncture delay, duration of the procedure, stroke onset to reperfusion delay
- Successful reperfusion defined by the modified Treatment In Cerebral Ischemia (mTICI) reperfusion scale of 2b or 3 (with a grade of 2b or 3 indicating reperfusion of > 50% of the affected territory)
- NIHSS by day 1 and day 7
- Stroke unit and hospital length of stay

- Perioperative complications by day 7 defined as pneumonia, acute cardiogenic pulmonary oedema, myocardial infarction, extra pulmonary infection, venous thromboembolism, new event of AIS, epilepsy, gastrointestinal bleeding or other symptomatic bleeding
- Malignant stroke evolution by day 7
- Symptomatic intracranial haemorrhage by day 7 defined as brain haemorrhage on imaging associated with an increase of at least 4 points in the NIHSS score
- Unexpected intensive care unit admission by day 7
- Mortality by day 7 and day 90
- Procedural feasibility score estimated by the radiologist and the anaesthesiologist and patient acceptability score

1. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1(1): 43-6.
2. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC medical research methodology* 2002; 2: 8.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018.
4. Nunn A, Bath PM, Gray LJ. Analysis of the Modified Rankin Scale in Randomised Controlled Trials of Acute Ischaemic Stroke: A Systematic Review. *Stroke research and treatment* 2016; 2016: 9482876.